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Predicting Septic Complications of Chemotherapy: An Analysis of 382 Patients Treated for Small Cell Lung Cancer without Dose Reduction after Major Sepsis

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The incidence and risk of septic complications in 382 patients treated for small cell lung cancer with combination chemotherapy at a single centre have been analysed. Full protocol doses were employed throughout with no dose reduction after episodes of severe or life-threatening sepsis (SLTS). 50 (13%) patients experienced 66 episodes of SLTS associated with 1978 cycles of chemotherapy (3.2% cycles affected). 20 (5.2%) patients died due to sepsis (SD) of whom only 4 had experienced SLTS with a previous cycle of treatment. The others died as a result of their first septic episode. A model comprising four variables, age (≤ 50 or > 50 years), Karnofsky performance status (KP ≤ 50 or > 50), treatment (two- or three-drug regimen) and previous sepsis (SLTS or no SLTS with previous cycles) was found to satisfactorily describe the incidence of SLTS and SD in the study population and once validated in another patient groups this model should allow identification of high-risk individuals before treatment starts. If so, we propose that high-risk patients (age > 50 years, KP ≤ 50, treatment with three-drug regimen) receive 50% of protocol doses in the first cycle of treatment with escalation to 75% and eventually 100% doses in subsequent cycles if sepsis does not supervene. Those with one or two risk factors present run a relatively low risk of SLTS or SD and we consider that full-dose chemotherapy should be used throughout in these individuals.
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INTRODUCTION

CANCER CHEMOTHERAPY is commonly attended by myelosuppression. This is reflected in reduced numbers of granulocytes and platelets in the peripheral blood and sometimes leads to infection or haemorrhage, both potentially fatal complications of treatment. Bleeding can usually be prevented if prophylactic platelet transfusions are employed when the platelet count falls to less than $20 \times 10^9/1$ and intravenous broad-spectrum antibiotic therapy often allows full recovery from even severe episodes of sepsis. However, sepsis related deaths do occur and non-fatal episodes of infection are a major contribution to the morbidity of cytotoxic chemotherapy. In efforts to reduce the incidence of these complications of treatment, physicians commonly reduce the dose of chemotherapy after an episode of severe infection and although such empiric alterations in planned dose are commonplace, there is no published data to either support or reject the hypothesis that dose reduction prevents further septic episodes. These issues are important since any reduction in

Table 1. Chemotherapy for 382 patients with small cell lung cancer in Manchester Lung Group studies 4–8

Study	*n*	Ifosfamide	Etoposide	Other
4	168	5 g/m² intravenous day 1	120 mg/m² intravenous day 1 240 mg/m² orally days 2 and 3	—
5	64	2 g orally days 1–3	100 mg orally days 1–8	—
6	51	5 g/m² intravenous day 1	120 mg/m² intravenous day 1 240 mg/m² orally days 2 and 3	Carboplatin 300 mg/m² intravenous day 1 Vincristine 1 mg day 14
7	38	5 g/m² intravenous day 1	120 mg/m² intravenous day 1 240 mg/m² orally days 2 and 3	Carboplatin 300 mgs/m² intravenous day 1 and vincristine 1 mg intravenous day 14 alternating with cisplatin 100 mg/m² intravenous day 1
8	61	5 g/m² intravenous day 1	120 mg/m² intravenous day 1 240 mg/m² orally days 2 and 3	Doxorubicin 50 mg/m² intravenous day 1

cytotoxic drug dosage will inevitably reduce the dose intensity of the regimen used and may jeopardise the potential for long-term survival[1].

In this paper we present the results of an analysis of septic events in a large group of patients receiving chemotherapy for small cell lung cancer (SCLC), none of whom had been subject to a reduction in chemotherapy dose following episodes of severe or life-threatening infection. A model to estimate the probability of septic complications occurring during chemotherapy based on patient characteristics, treatment type and incidence of severe sepsis with previous cycles of chemotherapy is also described. Finally, a strategy for maximising treatment in patients at low risk and for minimising toxicity in patients at high risk of sepsis is proposed.

PATIENTS AND METHODS

Between May 1984 and June 1988, 382 patients with histologically proven SCLC were treated at the two hospitals comprising the Manchester Lung Group (MLG) and are the subject of this analysis. A total of 1978 cycles of chemotherapy were administered according to five consecutive treatment protocols (MLG studies 4–8 inclusive). Studies 4 and 5 were two drug combinations (ifosfamide and etoposide) and the results are published [2,3]. Analysis of study 6, also published [4], was the first MLG regimen to include a platinum analogue and also featured mid-cycle vincristine. Study 7 was similar but included two platinum analogues [5] and study 8 was a three-drug but non-platinum containing combination [6]. Table 1 gives details of the chemotherapy administered. For each study a maximum of six cycles was planned at intervals of 21 days (studies 4, 5, 8), 28 days (study 6) or 21 days and 28 days on alternate cycles (study 7). Each cycle of chemotherapy was given on schedule if the total white cell count was $\geq 3.0 \times 10^9/l$ and the platelet count was $\geq 100 \times 10^9/l$. Prophylactic co-trimoxazole 960 mg twice daily was given for the duration of chemotherapy in all patients. Episodes of infection were graded by WHO criteria and for the purpose of this study, grades 3 (major infection requiring intervenous antibiotics, no hypotension) and 4 (major infection with hypotension) were included in a category of severe or life-threatening sepsis (SLTS). In studies 6 and 7, patients were seen at the hospital and had a full blood count performed on a weekly basis; patients with fever were admitted for immediate intravenous antibiotics whatever the blood count and those with mucositis or diarrhoea but no fever were also admitted for support and observation. Intravenous antibiotics were also commenced in these patients if the neutrophil count fell below $0.5 \times 10^9/l$ or if fever supervened. Death from sepsis (SD) was deemed to have occurred if at the time of death the patient had a bacteriologically proven infection or was receiving intravenous antibiotics for suspected infection (in the setting of fever and neutropenia) or had died at home at a time when severe neutropenia was likely.

None of the 382 patients in this study had been subject to a reduction in dose of chemotherapy for any reason. 2 patients (both in study 7) who were inadvertently given less than protocol dose after episodes of severe infection were excluded from the analysis and in study 5 one patient was excluded on the basis of histology review which revealed a non-small cell lung tumour. A total of 51 patients were treated in study 6 and are included in this analysis but published results only refer to the first 42 of these [4]. Similarly in study 4, 168 patients were treated and results for 163 without brain metastases at presentation have been reported [2]. Details of age, Karnofsky performance status (KP) [7, 8], Manchester prognostic score [9], renal function (serum creatinine), bone marrow infiltration, treatment received and septic complications, were retrieved from the computer held data base.

STATISTICS

The unit of study was one cycle of chemotherapy. For each cycle a trinomial response was defined as follows:

$$\Pr\{\text{SLTS}\} = P_1$$
$$\Pr\{\text{SD}\} = P_2$$
$$\Pr\{\text{No SLTS or SD}\} = P_3.$$

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Table 2. Incidence of septic events in Manchester Lung Group studies 4–8

Study	Patients (n)	Cycles of chemotherapy	Episodes SLTS (no. patients affected)	Septic deaths (no. patients with previous SLTS)	Total septic episodes (% cycles affected)
4	168	864	16 (14)	7 (0)	23 (2.7)
5	64	331	2 (2)	2 (0)	4 (1.2)
6	51	263	12 (9)	5 (2)	17 (6.5)
7	38	195	13 (12)	4 (2)	17 (8.7)
8	61	325	23 (13)	2 (0)	25 (7.7)
Total	382	1978	66 (50)	20 (4)	86 (4.3)

A multinomial logit type model [10] with the above nominal categories was used to see how patient characteristics prior to the first cycle, treatment type and the incidence of SLTS with any previous cycle influenced these response probabilities (or more precisely the ratios P_1/P_3, P_2/P_3). The responses on successive cycles for an individual will actually be correlated (estimated autocorrelation $=0.2$) but this is relatively small and models assuming independence of cycle responses are likely to be adequate [11]. Cycle to cycle independence has therefore been assumed in this study apart from the use of an explanatory variable indicating SLTS in any previous cycle.

In the text, odds SLTS refers to the odds of SLTS to no SLTS or SD (i.e.P_1/P_3). Similarly, odds SD refers to the odds of SD to no SLTS or SD (i.e.P_2/P_3).

RESULTS

The incidence of SLTS and SD by study is shown in Table 2. Overall, 50 (13%) patients had a total of 66 episodes of SLTS associated with 1978 cycles of chemotherapy giving a serious infective complication rate of 3.3% cycles administered. The incidence of SLTS by cycle number was 17 (cycle 1), 2 (cycle2), 13 (cycle 3), 17 (cycle 4), 8 (cycle 5) and 9 (cycle 6). 20 (5.2%) patients died from sepsis either in hospital (19 cases) or at home (1 case) and 11 autopsies were performed. 16 septic deaths occurred in the group of 332 patients without SLTS in previous cycles of treatment and, of these, 6 occurred with the first cycle, 4 with the second, 2 with the fourth and 4 with the fifth. A further 4 septic deaths occurred in patients who had experienced SLTS with preceding treatment.

In an effort to identify patients at risk of SLTS and or SD, seven variables of intuitive importance were selected for mathematical modelling. The possible effects of SLTS on the risk of a further septic event with a subsequent cycle of chemotherapy were of particular interest in this population, none of whom had been dose-reduced following the first episode of major sepsis. Age and Karnofsky performance status at presentation were also selected because our clinical experience suggested that frail, elderly individuals were at greater risk than stronger and younger ones. Factors possibly leading to increased myelosuppression were considered important and treatment, renal function and bone marrow involvement were included in this category. Finally, the effect of Manchester score, a prognostic scoring system for SCLC based on five pre-treatment variables [stage; KP; serum sodium; serum lactic dehydrogenase (LDH); serum bicarbonate] and which identifies patients as having a good, intermediate or poor prognosis was examined [9]. Four of these factors, treatment (two- or three-drug regimen $P<<0.0001$),KP score (≤ 50 or >50, $P=0.0008$),age (≤ 50 years or >50 years, $P=0.0008$) and prior sepsis (previous SLTS or no previous SLTS $P<0.001$), when taken together satisfactorily modelled the observed incidence of SLTS and SD in our data set (Fig. 1). Manchester score ($P=0.65$), pretreatment serum creatinine ($P=0.28$) and bone marrow involvement ($P=0.36$) had no additional significant effect on the incidence of SLTS or SD and were not considered further. The two variables, age and KP score, were initially considered in four groups of roughly equal frequencies. Having fitted a model, tests were performed to assess the possibility of merging adjacent groups and this resulted in the stated bandings of age (≤ 50 years or >50 years) and KP(≤ 50 or >50). Table 3 shows the 16 possible permutations of the four significant variables and the number of chemotherapy cycles associated with SLTS or SD in each group. One striking feature is that 1887 cycles of chemotherapy were administered in the setting of no SLTS in previous cycles (groups 1–8) but only 85 cycles were given following the first episode of SLTS (groups 9–16). The reasons for this disparity are 2-fold. First, only 50 of 382 patients experienced at least one episode of SLTS (and so were eligible for further chemotherapy after this event) and second, 16 of these 50 patients terminated treatment early due to a variety of reasons and summarised in Table 4.

Table 5 shows the estimated probabilities of SLTS, SD or no SLTS/SD according to the distribution of the four modelled risk factors. It is clear that for all groupings Pr(SLTS) is always higher than Pr(SD) and that the probability of both these outcomes increases as the number of pretreatment risk factors (age $>$ 50 years, KP $\leq$ 50, three-drug regimen) accumulate. Moreover, if SLTS occurs the probability of SLTS or SD with subsequent cycles of chemotherapy is correspondingly increased (assuming age, KP and treatment regimen remain constant). Overall, the estimated risk of a serious septic event in the population is quite small with six of eight groups having an estimated probability of completing six cycles without any serious septic event of greater than 0.7. However, for a patient aged $>$ 50 years, with a KP $\leq$ 50 and treated with a three-drug combination the estimated probability of completing chemotherapy without SLTS or SD is halved (0.35).

The same data is expressed differently in Table 6 which shows the calculated effect of each adverse factor on increasing the odds of SLTS or SD in a future cycle of chemotherapy. Treatment with a three-drug regimen and SLTS in a previous

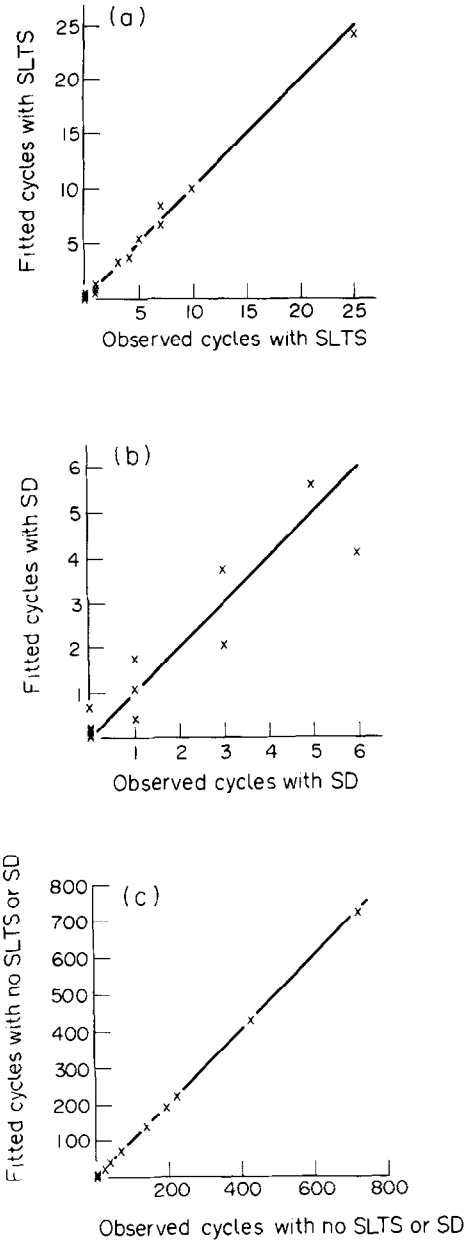

Fig. 1. Plots of observed to predicted incidence of severe or life-threatening sepsis (SLTS, a), septic death (SD,b) and no SLTS or SD (c). Predicted incidence is derived from a model comprising age, KP, treatment regimen and previous SLTS (see text).

cycle each raise the odds of SLTS in subsequent cycles by about 5-fold and by 25-fold when both factors are present. Similarly, KP ≤ 50 and age > 50 years each have the effect of raising the odds of SLTS by about 3-fold. The combination of all four adverse factors increases the risk of SLTS by a factor of 196. Age > 50 years has the greatest effect on raising the odds of SD (by a factor of 6.2) followed by SLTS with a previous cycle of treatment (× 4.2), KP ≤ 50 (× 3.6) and the use of a three-drug regimen (× 2.5). It is of interest that according to our model treatment has the greatest effect of all the adverse factors on increasing the odds of SLTS but the least effect on the odds of SD. Previous SLTS has a very similar effect on both outcomes (4–5-fold).

DISCUSSION

Severe and life-threatening infections are a feature of cytotoxic chemotherapy for cancer and it is usual for subsequent cycles of treatment to be administered at reduced dose. This practice is based on two assumptions. The first is that further episodes of infection are more likely after the first event than if previous cycles were sepsis-free. The second is that dose reduction will reduce the risk of a second serious infection occurring and, more importantly, prevent a septic death. However, published data in this area are not available. These issues are important because if smaller doses of chemotherapy are administered the planned dose intensity will inevitably be reduced and for chemosensitive tumours, the chance of long-term survival may be compromised[1]. In this paper we present the analysis of an unconventional policy employed in the treatment of SCLC whereby an episode of severe or life-threatening sepsis did not result in dose reductions in subsequent cycles of chemotherapy.

Overall, 50 (13%) of 382 patients experienced at least one SLTS and 20 (5.2%) died due to sepsis (Table 2). Earlier studies (4 and 5) were associated with a lower incidence of sepsis (SLTS or SD) than more recent ones (6, 7 and 8) and this is in keeping with the addition of myelosuppressive drugs (especially carboplatinum) to the treatment regimens. There was a more than 7-fold difference in frequency of septic events between patients in study 5 treated with oral ifosfamide and etoposide and those in study 7, receiving ifosfamide, etoposide, carboplatinum and vincristine alternating with cisplatinum (Table 2).

The effect of seven factors on the subsequent incidence of serious septic complications have been examined. Five (age, bone marrow infiltration, renal function, KP score, and Manchester score) are pre-treatment variables, one (two- or three-drug regimen) relates to the treatment itself and another (previous SLTS) depends on exposure to at least one cycle of the same chemotherapy. Factors were selected intuitively.

Age, KP, treatment and previous sepsis contributed power to the model defining probability of SLTS or SD in subsequent cycles of chemotherapy. We were surprised that renal function did not contribute additional information but it is possible that a more sensitive measure of renal function than serum creatinine would have produced a different result. Bone marrow status as assessed by aspirate and trephine biopsy was also unhelpful but only 20 of 273 patients tested were positive which suggests a very high false-negative rate for a disease considered to be widely metastatic from an early stage.

According to the model each combination of variables predicts a certain probability of SLTS or SD with the risk increasing as another adverse factor is added (Table 5). It should be noted, however, that for even the worst group (age > 50 years, KP ≤ 50, three-drug regimen, previous SLTS) the probability of death from sepsis is still less than 0.1. Looked at another way each variable increases the odds of SLTS or SD occurring to no SLTS or SD by a certain factor (Table 6). Treatment has the largest effect on the odds of SLTS (×4.9) but the smallest effect on odds of SD (×2.5) where age is the most important (×6.2). This accords well with the idea that sepsis occurs because of neutropenia (which may be more or less severe depending on treatment) but that patient characteristics determine whether or not the individual is able to survive the effects of sepsis once present. The commonly held view that sepsis is more likely after a previous episode is supported by this study with the odds of SLTS and SD increased by a very similar amount (4.8-fold and 4.2-fold, respectively) after SLTS with any previous cycle (not only the immediately preceding one). It is also of note that in

Table 3. Incidence of SLTS/SD or no SLTS/SD in each of 16 risk factor groupings

Group	Three-drug regimen	KP ≤50	Age >50	Previous SLTS	Total cycles	Cycles of chemotherapy with			Cycles with SLTS/SD(%)
						No SLTS/SD	SLTS	SD	
1	−	−	−	−	139	138	1	0	0.7
2	−	+	−	−	69	68	1	0	1.4
3	−	−	+	−	734	724	7	3	1.4
4	+	−	−	−	194	190	3	1	2.0
5	−	+	+	−	230	217	7	6	5.6
6	+	+	−	−	21	20	1	0	4.8
7	+	−	+	−	456	426	25	5	6.6
8	+	+	+	−	44	38	5	1	13.6
9	−	−	−	+	0	0	0	0	—
10	−	+	−	+	5	5	0	0	0
11	−	−	+	+	8	7	1	0	12.5
12	+	−	−	+	1	1	0	0	0
13	−	+	+	+	10	9	1	0	5.3
14	+	+	−	+	2	2	0	0	0
15	+	−	+	+	49	36	10	3	26.5
16	+	+	+	+	10	5	4	1	50.0

+ Signifies presence and − signifies absence of a particular risk factor.
Note: According to the table the sum of total cycles given to 16 groups is 1972. This is six fewer than stated in the text and is due to a missing value for KP in 1 patient who received six cycles of chemotherapy.

Table 4. Reasons for early discontinuation of chemotherapy in 16 patients experiencing SLTS

Reasons for less than six cycles	Patients (*n*)
Progressive disease (after cycles 1,2,4,5)	4
Patient decision not to continue treatment (after cycles 4,4,5)	3
Renal failure (after cycles 1,3)	2
Severe depression (after cycles 1,5)	2
Incorrectly assigned to study	1
No venous access (after cycle 4)	1
Recto-vaginal fistula due to diverticular disease (after cycle 2)	1
Died at home of unknown cause (after cycle 1)	1
Prolonged neutropenia (after cycle 1) in 71-year-old woman	1

common with age, KP and treatment, this effect is independent of other factors and is not simply a marker of other adverse factors in the same individual.

Major sepsis is an important cause of morbidity and mortality in cancer chemotherapy and strategies are required to minimise these complications without jeopardising the efficacy of treatment. Dose reduction after an initial episode of SLTS is commonly employed but even if completely successful this policy does not solve the problem of patients dying as a consequence of their first septic event (16 of 20 patients in this study). Identification of high-risk individuals before starting treatment is therefore required and the model described here, once validated on another patient population, may allow this.

For any patient, age and KP are fixed and the only negotiable risk factor for an individual already vulnerable to sepsis on account of age >50 years and KP ≤50 is the treatment chosen. By using less myelosuppressive chemotherapy in these circumstances our model predicts a lower risk of sepsis than if more myelotoxic treatment were employed. A logical strategy to both maximise treatment and minimise septic complications might therefore consist of first selecting treatment (three-drug or two-drug) on the basis of prognostic scoring which, in the Manchester system, divides patients into good, intermediate and poor groups [9]. Second, individuals within each prognostic group at particular risk of sepsis on account of age > 50 and KP ≤ 50 could be identified and treated with say 50% of protocol dose in the first cycle. If this proved successful (no SLTS or SD) the second dose could be escalated to 75% and the third to 100% protocol doses, again subject to an absence of septic complications in the preceding cycle. Stepwise dose escalation in at-risk individuals is the inverse of current practice where dose reduction is generally employed after the first episode of sepsis and which takes no account of patients at risk of septic death with the first cycle of treatment. In our experience chemotherapy for SCLC normally results in a higher KP score at the completion of treatment than at presentation [2–6] and although the effect of changing KP has not been examined in this analysis it is possible that as performance status improves, the risk of developing a septic complication is reduced so that eventually full doses can be employed even in initially high-risk individuals. However, randomised clinical trials are required to test the effectiveness of this and other approaches (such as the use of haemopoietic growth factors) in reducing the incidence of septic events.

To our knowledge, this is the first study to analyse risk factors for sepsis in patients undergoing cytotoxic chemotherapy. The policy of no dose reduction allowed us to examine and confirm the suspicion that second or subsequent septic events are more likely after the first episode than if previous cycles are sepsis-free. We are unable to say whether dose reduction after the first episode of major sepsis reduces the risk of further SLTS or SD and this question can only be addressed by centres with a consistent policy of dose reduction. However, we have been able

Table 5. Estimated probability (Pr) per cycle of SLTS, SD or no SLTS/SD according to treatment, KP, age and incidence of previous SLTS

Treatment	KP	Age	No previous SLTS Pr (SLTS)	No previous SLTS Pr (SD)	No previous SLTS Pr (no SLTS/SD)	Previous SLTS Pr (SLTS)	Previous SLTS Pr (SD)	Previous SLTS Pr (no SLTS/SD)	Pr of completing six cycles without SLTS/SD	Pr of completing six cycles without SD
2 drug	High	Young	<0.01	<<0.01	0.99	0.02	<0.01	0.98	0.97	0.99
2 drug	Low	Young	0.01	<0.01	0.99	0.04	0.01	0.95	0.93	0.98
2 drug	High	Old	0.01	0.01	0.98	0.05	0.02	0.93	0.90	0.97
3 drug	High	Young	0.02	<0.01	0.98	0.08	<0.01	0.91	0.89	0.99
2 drug	Low	Old	0.03	0.02	0.95	0.12	0.06	0.82	0.75	0.88
3 drug	Low	Young	0.04	0.01	0.95	0.17	0.03	0.80	0.73	0.95
3 drug	High	Old	0.05	0.01	0.93	0.21	0.04	0.75	0.67	0.91
3 drug	Low	Old	0.12	0.04	0.84	0.37	0.10	0.52	0.35	0.71

Age is recorded as young (≤50 years) or old (>50 years) and KP as low (≤50) or high (>50).

Table 6. Effect of four risk factors on the odds of SLTS to no SLTS/SD and SD to no SLTS/SD

Outcome	Variable	Co-efficient estimate	Multi-plication factor	Approx. 95% confidence intervals
SLTS	Constant 1	−5.626		
	Treatment (0=2-drug) (1=3-drug)	1.580	4.9	(2.7,8.8)
	KP (0=>50) (1=≤50)	0.949	2.6	(1.4,4.7)
	Age (0=≤50) (1=>50)	1.176	3.2	(1.4,7.7)
	Previous SLTS (0=No) (1=Yes)	1.570	4.8	(2.5,9.2)
SD	Constant 2	−7.085		
	Treatment (0=2-drug) (1=3-drug)	0.930	2.5	(0.96,6.7)
	KP (0=>50) (1=≤50)	1.288	3.6	(1.4,9.5)
	Age (0=≤50) (1=>50)	1.817	6.2	(0.81,47.0)
	Previous SLTS (0=No) (1=Yes)	1.438	4.2	(1.3,14.0)

The odds of either SLTS or SD occurring in patients with more than one adverse feature are calculated by taking the product of individual multiplication factors (for example, the odds of SLTS to no SLTS/SD in a patient with KP≤50, a history of previous SLTS and treated with a three-drug regimen is 2.6×4.8×4.9, i.e. 61.1 times the equivalent odds for a patient in the same age group with KP>50, no history of previous SLTS and treated with a two-drug regimen).

to construct a model which satisfactorily describes the incidence of SLTS or SD in our population and if validated in another patient group, prospective identification of high-risk individuals should be possible. If so, strategies to reduce risk might be applicable and a reduced starting dose with stepwise escalation to eventual full-dose treatment is proposed for patients older than 50 years, with a KP of 50 or less and due to receive a more myelosuppressive regimen. For others at low or intermediate risk of sepsis (one or two risk factors present) we suggest that full protocol doses are employed from the outset. Even if SLTS supervenes we argue that full doses should be continued because the risk of further SLTS or SD in these circumstances remains relatively low (Table 5) and a greater threat to survival may be posed by an inadequately treated chemosensitive tumour.

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